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A Simple One-Pot Electrochemical Procedure for the Preparation of Novel 3,4-aminophenol Derivatives Possessing Anti-stress Oxidative Properties.

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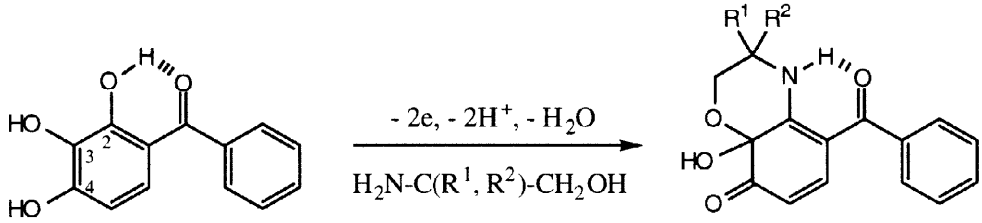
Abstract : The conversion of 3,4-diphenol derivatives to novel 3,4-aminophenol derivatives possessing anti-stress oxidative properties could be achieved in methanol by a simple one-pot procedure, via the reaction of a transient electrogenerated 3,4-quinone. © 1998 Elsevier Science Ltd. All rights reserved.

A few years ago, we described the synthesis of novel 1,4-benzoxazin-8-one derivatives possessing pharmacological properties [1] via the reaction in methanol of electrochemically or chemically generated orthoquinones with amino alcohols (scheme). By varying the nature of the amino alcohol, we established that neither R^1 nor R^2 could be an hydrogen atom. This condition appeared to constitute a prerequisite to the formation of 1,4-benzoxazin-8-one derivatives [2].



1 R^1 and R^2 = Me or CH_2OH

Scheme

Nevertheless, in the presence of amino alcohols derived from natural amino acids (H_2N-CHR-CH_2OH), a competing reaction arose implying a nucleophilic attack of the transient 3,4-quinone species at the 3-position rather than at the 2-position. At that point, we focused our attention on this competing reaction which constituted a key step in the synthesis of novel 3,4-aminophenol derivatives.

A survey of the literature revealed that the aromatic nucleophilic substitution reaction of hydroxy groups by amino groups has remained restricted. Two general approaches could be essentially used for the conversion of a phenol derivative into the corresponding aniline : a) the direct reaction with amine that requires very high temperature; b) an indirect method in which the phenolic ring is successively dearomatized, treated with amine and rearomatized. The latter method involved the initial transformation of the phenol derivative into an activated compound prior to breaking of the carbon-oxygen bond [3-5]. For instance, in the *Bucherer* reaction, replacement of hydroxy by amino groups occurred via the keto tautomer of the phenol [6]. However, all these

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reactions required high temperatures [7]. In the present work, we wish to report an electrochemical procedure we feel to be simple for the conversion of aromatic hydroxy compounds to the corresponding amino compounds. The synthesis of 3,4-aminophenol derivatives could be accomplished through the reaction of an electrogenerated 3,4-quinone with amino alcohols.

Compound **1** was oxidized at room temperature, in methanol, in the presence of lithium perchlorate as the supporting electrolyte and an excess of amino alcohols, in a 3-compartment cell, at a mercury anode and platinum cathode, by controlled potential electrolysis [8]. When the potential of the mercury pool was fixed at + 0.05 V vs. saturated calomel electrode (s.c.e.), i.e. at a potential immediately following the anodic peak observed in cyclic voltammetry, a coulometric value of 2.0 ± 0.1 was found for the number of electrons (n) involved in the oxidation of one molecule of **1** into the transient 3,4-quinone species. This was converted into an unstable product which probably polymerized since no defined product could be isolated after preparative anodic electrolysis. Nervertheless, we thought that the unstable oxidation product could be stabilized through a reduction step, provided that the potential of the mercury cathode was fixed at - 1.5 V s.c.e., i.e. at a potential following the cathodic peak that appeared in the course of the anodic electrolysis. Accordingly, after exhaustive anodic electrolysis, the resulting oxidized solution was electrochemically reduced. Finally, preparative scale electrolysis allowed the isolation of 3,4-aminophenol derivatives **2-7** as the major product (entries 1-6 of the table).

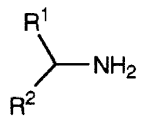
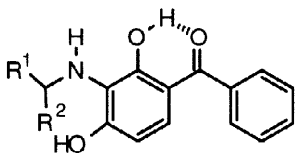
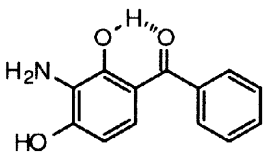
In order to explore further the scope of this electrochemical procedure with respect to synthetic applications, we investigated the behaviour of **1** in the presence of amines (entries 7-11). Amines behaved similarly except that the production of **13** markedly increased at the expense of the formation of 3,4-aminophenol derivatives **8-12**. Even, **13** became the major compound in two cases (entries 10-11). This result indicated that **13** likely stemmed from the hydrolysis of a transient species produced in the course of the anodic electrolysis. Accordingly, in the case of benzhydrylamine (entry 7), beside compounds **8** and **13**, benzophenone was obtained in roughly 20% yield, as well as the imine derivative $Ph_2C{=}N\text{-}CHPh_2$ isolated in 15% yield. In this connection, preparative and mechanistic studies related to the reaction of orthoquinones of biological interest (coenzymes PQQ, TTQ) with amines have been previously reported [9, 10]. Mechanistic investigations are under way in our laboratory to provide a better understanding of the reaction pathway enabling the conversion of 3,4-diphenol derivatives to 3,4-aminophenol derivatives, via the reaction of the transient electrogenerated 3,4-quinones with amines.

In summary, we have developed a simple one-pot electrochemical procedure for the synthesis of novel 3,4-aminophenol derivatives. The key step consisted of the reaction of the electrogenerated 3,4-quinone with amino alcohols or amines. Note that other existing methods would be inefficient owing to the easy oxidation of both the substrate and the product. Furthermore, our procedure could be extended to all substrates exhibiting $(HO)_3C_6H_2\text{-}CO\text{-}R$ skeleton, with R = alkyl, OR', NHR' for example.

In the course of preparing molecules of pharmacological interest, we have investigated the protective activity *in vitro* of compounds **2-13** against oxidative stress. Reflecting these properties, 3,4-aminophenol derivatives were identified as significantly active on HT-22 hippocampal neurons. In order to confirm their anti-stress oxidative properties *in vivo*, larger amounts of these compounds are necessary. So, efforts to accomplish the total synthesis of 3,4-aminophenol derivatives are in progress in our laboratory.

Table

Products and Yields of Controlled Potential Electrolyses of **1** in methanol containing an excess of amino alcohol or amine. E_{ox} = + 0.05 V s.c.e. ; E_{red} = - 1.5 V s.c.e.

Entry					
	R^1	R^2	Product	Yield %	**13**[a] Yield %
1	CH_2OH	Bu^t	**2**	65	-
2	CH_2OH	Pr^i	**3**	57	8
3	CH_2OH	Me	**4**	60	5
4	CH_2OH	CH_2OH	**5**	55	10
5	CH_2OH	Bzl	**6**	55	10
6	CH_2OH	H	**7**	60	22
7	Ph	Ph	**8**	37	23
8	Me	Me	**9**	50	17
9	Pe^i	H	**10**	35	30
10	Me	Pr^i	**11**	31	40
11	Pr^i	Pr^i	**12**	15	55

Abbreviations : tertiobutyl (Bu^t), isopropyl (Pr^i), isopentyl (Pe^i), Benzyl (Bzl).

[a] *Yield of compound **13** was probably higher than indicated because significant amounts were lost upon column chromatography due to its easy oxidation.*

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[8] A typical procedure was as follows : A solution of 2,3,4-trihydroxybenzophenone **1** (0.11g ; 0.5 mmol), lithium perchlorate (0.53g ; 5 mmol) and amino alcohol or amine (5 mmol) in methanol (250 mL) was oxidized under nitrogen at room temperature at + 0.05 V s.c.e. After exhaustive oxidation, i.e. when a steady-state minimum value of the current was recorded, the resulting solution was immediately reduced after the potential of the mercury pool was switched to - 1.5 V s.c.e. After exhaustive cathodic electrolysis, the solution was poured into a molar acetic acid-buffered aqueous solution of pH ~ 4.5 (100 mL). The resulting hydroalcoholic solution was concentrated to 100 mL under reduced pressure at 40°C and extracted with ethyl acetate (200 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure at 40°C. The residue was chromatographed on silica, to give the expected 3,4-aminophenol derivatives.

3-[(2-hydroxy-1-tertiobutyl)-ethylamino]-2,4-dihydroxybenzophenone **2** : ^{1}H NMR (300 MHz, DMSO D_6) : δ 1.00 (s, 9H, Me, Bu^t), 3.30 (m, 1H, CH_2OH), 3.45 (m, 1H, CH-N), 3.60 (m, 1H, CH_2OH), 3.90 (broad s, 1H, NH, D_2O exchanged), 6.40 [d, 1H, H(5), J = 8 Hz], 6.85 [d, 1H, H(6), J = 8 Hz], 7.50 [m, 5H, benzoyl (1)], 12.80 [broad s, 1H, OH(2), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6) : δ 28.0 (Me, Bu^t), 35.8 (Cq, Bu^t), 63.0 (CH_2OH), 65.1 (CH-N), 109.2 (C-5), 113.1 (C-1), 126.4 (C-6), 126.6 (C-3), 129.4 [CH, meta, benzoyl (1)], 129.6 [CH, ortho, benzoyl (1)], 132.5 [CH, para, benzoyl (1)], 139.2 [Cq, benzoyl (1)], 155.0 and 155.1 (C-2 and C-4), 200.1 [CO, benzoyl (1)]. MS (DCI) : m/z = 330 (MH^+).

3-amino-2,4-dihydroxybenzophenone **13** : ^{1}H NMR (300 MHz, DMSO D_6) : δ 6.40 [d, 1H, H(5), J = 8 Hz], 6.75 [d, 1H, H(6), J = 8 Hz], 7.60 [m, 5H, benzoyl (1)], 10.20 [broad s, 1H, OH(4), D_2O exchanged], 12.20 [broad s, 1H, OH(2), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6) : δ : 108.3 (C-5), 113.0 (C-1), 124.0 (C-6), 125.0 (C-3), 129.3 [CH, meta, benzoyl (1)], 129.7 [CH, ortho, benzoyl (1)], 132.3 [CH, para, benzoyl (1)], 139.3 [Cq, benzoyl (1)], 151.8 and 151.9 (C-2 and C-4), 200.9 [CO, benzoyl (1)]. MS (DCI) : m/z = 230 (MH^+); m/z = 247 (MNH_4^+).

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